OGG1 Polymorphisms and Breast Cancer Risk

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Abstract

The role of oxidative stress in breast cancer risk is still unclear. *OGG1* encodes an 8-oxoguanine DNA glycosylase/AP lyase that catalyzes the removal of 8-oxodeoxyguanosine from DNA. 8-Oxodeoxyguanosine, the most abundant lesion generated by oxidative stress, is highly mutagenic. Environmental sources of oxidative stress, such as alcohol consumption, cigarette smoking, high body mass index (BMI), and low fruits and vegetables intake, may modify the association of genetic polymorphisms with breast cancer risk. We investigated the association between three genetic polymorphisms in *OGG1* ($Ser^{326}Cys$, 7143A/G, and 11657A/G) and breast cancer risk among 1,058 cases and 1,102 controls participating in the Long Island Breast Cancer Study Project. No associations were observed between individual *OGG1* polymorphisms, haplotypes, or diplotypes and breast cancer. The association between having at least one variant allele and breast cancer risk was stronger among moderate alcohol drinkers for $Ser^{326}Cys$ [odds ratio (OR), 1.82; 95% confidence interval (95% CI), 1.06-3.10] relative to nondrinkers with the wild-type genotype and among those with higher BMI for 7143A/G (OR, 1.47; 95% CI, 1.10-1.96) and for 11657A/G (OR, 1.41; 95% CI, 1.05-1.88), relative to women with BMI < 25 kg/m^2 and the wild-type genotype. However, the patterns were not seen for all three single nucleotide polymorphisms (SNP) nor were there any clear allele dose associations; only one interaction was statistically significant, assuming a multiplicative model (11657A/G, $P_{interaction} = 0.04$). In summary, although we found some differences between the three *OGG1* SNPs and breast cancer risk among moderate alcohol drinkers and women with higher BMI, replication of these results is needed to rule out spurious findings. In addition, data on functionality of these polymorphisms are crucial to understand if these modest differences are important. (Cancer Epidemiol Biomarkers Prev 2006;15(4):811–5)

Introduction

Oxidative DNA damage induced by reactive oxygen species plays an important role in a number of pathologic processes, including carcinogenesis. 8-Oxodeoxyguanosine, the most abundant lesion generated by oxidative stress from the environment and normal cellular metabolism, is highly mutagenic resulting in GC-to-TA transversions (1). 8-Oxodeoxyguanosine lesions can be excised by 8-oxoguanine DNA glycosylase/AP lyase, the enzyme encoded by *OGG1*. Alternative splicing results in the formation of several splice variants that are classified into two major types (2). Type 1 splice variants end with exon 7, whereas type 2 ends with exon 8. All variants share a common NH_2-terminal region that is essential for mitochondrial localization.

Most studies analyzing the association of genetic variability in *OGG1* with cancer susceptibility and gene-environment interactions have concentrated on a single nucleotide polymorphism (SNP) located at codon 326 in exon 7 ($Ser^{326}Cys$). Thus far, two studies have analyzed the *OGG1* $Ser^{326}Cys$ polymorphism and breast cancer risk (3, 4). No significant association was observed either among 425 Danish cases and 434 controls, or 475 Korean and Japanese cases and 500 controls. In the latter study, interactions between the polymorphism and known environmental risk factors for breast cancer were analyzed; however, no significant associations were observed. Two other *OGG1* SNPs, 7143A/G and 11657A/G, located further downstream in a noncoding region, were found to be associated with prostate cancer risk (5).

In the present study, the association between three *OGG1* sequence variants ($Ser^{326}Cys$, 7143A/G, and 11657A/G) analyzed as genotypes, haplotypes, and diplotypes and breast cancer risk, as well as gene-environment interactions with known breast cancer risk factors, including factors known to be associated with oxidative damage, was studied.

Materials and Methods

Subjects. The main purpose of the Long Island Breast Cancer Study Project was to investigate whether environmental factors, specifically polycyclic aromatic hydrocarbons and organochlorine pesticides, were associated with breast cancer risk. Details of the study design were described previously (6). Briefly, eligible cases were women residing in Nassau or Suffolk counties in New York, who spoke English, and were newly diagnosed with *in situ* or invasive breast cancer between August 1, 1996 and July 31, 1997. Population-based controls were identified using random digit dialing (<65 years of age) and Health Care Financing Administration rosters and frequency matched to the expected age distribution of the cases by 5-year age group.

Exposure assessment. The main questionnaire assessed information on known and suspected risk factors for breast cancer, including passive and active cigarette smoking, lifetime alcohol use, menstrual and reproductive histories, hormone use, body size by decade of adult life, lifetime participation in

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recreational activities, prior medical history, and family history of breast cancer (http://epi.grants.cancer.gov/LIBCSP/projects/Questionnaire.html). Usual dietary intake in the year before the interview was assessed using a self-administered food frequency questionnaire (7). Of the eligible women who completed the main questionnaire (1,508 cases and 1,556 controls), 2,243 donated blood samples (1,102 cases and 1,141 controls). Stored DNA samples were available for 1,058 cases (70% of participating cases) and 1,102 controls (71% of participating controls). Blood donation at interview was associated with race, cigarette smoking, alcohol use, use of oral contraceptives and hormone replacement therapy, lactation, and mammography (8).

OGG1 genotyping. Genotyping analysis was done on mononuclear cell DNA using a template-directed dye-terminator incorporation assay with fluorescence polarization detection as described by Chen et al. (9). Details are in the Supplementary Material. To enumerate the error from DNA isolation, aliquoting, plating, and genotyping, 170 (8%) blinded case pairs (before and after chemotherapy) were included. Concordance based on the κ statistic was >90% for all three *OGG1* loci.

Statistical analysis. We compared observed and expected genotype frequencies among the controls from the Hardy-Weinberg equilibrium theory (10). χ^2 tests for categorical variables were used to assess case-control differences in frequencies of genotypes (11). Genotyping data for the three SNPs were imported into Stephen's PHASE, version 2.1, program to infer the phase of alleles (i.e., haplotypes; refs. 12, 13). The output from the program was a haplotype pair (or diplotype) assigned to each woman and the posterior probability of each assignment. For each woman, we selected the haplotype pairs with the highest posterior probability.

Unconditional logistic regression with SAS version 9.1 was used to estimate odds ratios (OR) and corresponding 95% confidence intervals (95% CI; ref. 11). All models were adjusted for age at reference (defined as age at diagnosis for cases and age at identification for controls). Covariates considered as potential confounders included menopausal status, first-degree family history of breast cancer, body mass index (BMI), physical activity, fruits and vegetables intake, race, family history of breast cancer, lifetime alcohol intake, active smoking status, age at menarche, parity, and menopausal status and were included in the final model if their inclusion changed the exposure estimate by >10%. None of these covariates confounded the estimates on exposure by 10%, but we present both the age-adjusted results and the results from the saturated model for comparison.

We also further evaluated interaction (both additive and multiplicative) by using indicator terms for those with the genotype only, exposure only, and those with both the genotype and exposure of interest (14). If the relative risk, as approximated by the OR, for both genotype and exposure was greater than the relative risk of either factor alone added together minus 1, we concluded that there was evidence of a positive additive interaction.

Results

The distribution of the *OGG1* genotypes is shown in Table 1. The frequency of Ser^{326}Cys *CC*, *GC*, and *GG* genotypes were 59.7%, 35.2%, and 5.0%, respectively. The 7143A/G genotype frequencies of *AA* (73.0%), *AG* (24.6%), and *GG* (2.4%) were similar to those for 11657A/G: 74.2% (*AA*), 23.6% (*AG*), and 2.2% (*GG*). All three SNPs were in Hardy-Weinberg equilibrium in controls ($P = 0.85$, $P = 0.56$, $P = 0.53$, respectively). No differences in the distribution of genotypes between cases and controls were observed for any of the SNPs. Estimation of haplotypes resulted in three common (i.e., >10%) haplotypes: CAA (62.7%), GAA (22.3%), and CGG (13.6%). The χ^2 tests for linkage disequilibrium between the three SNPs were all significant ($P < 0.0001$). Lewontin's *D* between Ser^{326}Cys and 7143A/G, between Ser^{326}Cys and 11657A/G, and between 7143A/G and 11657A/G were −0.4755, −0.4709, and 0.4955, respectively. There were no significant differences in haplotype frequencies between cases and controls. Diplotype analysis also did not indicate any association between *OGG1* diplotypes and breast cancer risk (Table 1).

Table 1. Distribution of *OGG1* genotypes and breast cancer risk (age-adjusted ORs for three SNP *OGG1* haplotypes and diplotypes in relation to breast cancer)

Genotype or haplotype			Cases, N (%)	Controls, N (%)	OR* (95% CI)	OR† (95% CI)
Ser^{326}Cys(C/G) genotype						
CC			615 (59.1)	653 (59.7)	1.00	1.00
GC			375 (36.0)	385 (35.2)	1.04 (0.87-1.24)	1.06 (0.88-1.28)
GG			51 (4.9)	55 (5.0)	0.99 (0.66-1.47)	1.01 (0.68-1.52)
7143A/G genotype						
AA			750 (71.9)	797 (73.0)	1.00	1.00
GA			264 (25.3)	269 (24.6)	1.03 (0.85-1.26)	1.01 (0.58-1.77)
GG			29 (2.8)	26 (2.4)	1.20 (0.70-2.06)	1.70 (0.45-6.51)
11657A/G genotype						
AA			775 (73.2)	818 (74.2)	1.00	1.00
GA			260 (24.6)	260 (23.6)	1.05 (0.86-1.28)	1.04 (0.59-1.84)
GG			23 (2.2)	24 (2.2)	1.04 (0.58-1.87)	0.65 (0.16-2.67)
Haplotype						
CAA			1,326 (62.1)	1,393 (62.7)	1.00	
GAA			474 (22.2)	495 (22.3)	1.01 (0.87-1.17)	
CGG			298 (14.0)	302 (13.6)	1.03 (0.86-1.23)	
All others			36 (1.7)	32 (1.4)	1.19 (0.74-1.94)	
Diplotype						
Ser^{326}Cys	7143A/G	11657A/G				
CC	AA	AA	411 (38.5)	441 (39.7)	1.00	
CG	AA	AA	303 (28.4)	308 (27.7)	1.06 (0.86-1.31)	
CC	GA	GA	182 (17.1)	179 (16.1)	1.08 (0.84-1.38)	
CG	GA	GA	66 (6.2)	73 (6.6)	0.96 (0.67-1.38)	
GG	AA	AA	49 (4.6)	55 (5.0)	0.96 (0.64-1.44)	
All others			56 (5.3)	55 (5.0)	1.11 (0.75-1.66)	

*ORs are adjusted for age (continuous).
†ORs are adjusted for age and simultaneously adjusted for three SNPs.

Table 2. Multivariate-adjusted OR and 95% CI of alcohol interaction for *OGG1* polymorphisms

Genotype	Lifetime Alcohol Intake (grams/day)	Cases, N	Controls, N	OR* (95%CI)	OR† (95%CI)
$Ser^{326}Cys$(C/G)					
CC	Never‡	234	234	1.00	1.00
GC + GG	Never	157	165	0.97 (0.73-1.29)	0.98 (0.72-1.33)
CC	<15	281	317	0.93 (0.73-1.19)	0.97 (0.74-1.26)
GC + GG	<15	203	220	0.97 (0.74-1.26)	1.03 (0.77-1.37)
CC	15-30	67	52	1.38 (0.92-2.08)	1.38 (0.87-2.19)
GC + GG	15-30	49	30	1.69 (1.04-2.77)	1.82 (1.06-3.10)
CC	≥30	33	49	0.73 (0.45-1.19)	0.89 (0.53-1.51)
GC + GG	≥30	17	25	0.73 (0.38-1.39)	0.81 (0.41-1.62)
7143A/G genotype					
AA	Never‡	295	293	1.00	1.00
GA + GG	Never	99	104	0.95 (0.69-1.31)	0.98 (0.69-1.39)
AA	<15	337	400	0.88 (0.71-1.10)	0.93 (0.73-1.18)
GA + GG	<15	145	138	1.07 (0.80-1.42)	1.11 (0.82-1.51)
AA	15-30	81	58	1.46 (1.00-2.12)	1.49 (0.98-2.27)
GA + GG	15-30	36	25	1.50 (0.88-2.58)	1.58 (0.86-2.89)
AA	≥30	37	45	0.88 (0.55-1.40)	0.93 (0.56-1.53)
GA + GG	≥30	13	28	0.50 (0.25-0.99)	0.72 (0.34-1.52)
11657A/G genotype					
AA	Never‡	308	311	1.00	1.00
GA + GG	Never	89	93	0.97 (0.70-1.35)	0.95 (0.66-1.36)
AA	<15	351	400	0.93 (0.75-1.16)	0.96 (0.76-1.22)
GA + GG	<15	143	140	1.05 (0.79-1.40)	1.09 (0.81-1.48)
AA	15-30	80	60	1.41 (0.97-2.05)	1.47 (0.97-2.23)
GA + GG	15-30	37	23	1.73 (1.00-2.99)	1.68 (0.91-3.10)
AA	≥30	36	46	0.85 (0.53-1.35)	0.88 (0.54-1.46)
GA + GG	≥30	14	28	0.55 (0.28-1.07)	0.78 (0.37-1.63)

*ORs are adjusted for age.
†ORs are additionally adjusted for lifetime alcohol intake, active smoking status, menopausal status, first degree family history, BMI, physical activity, and fruits and vegetables consumption.
‡Reference group.

Table 2 shows the results of the alcohol interaction analysis for the *OGG1* polymorphisms. A priori, heterozygous and homozygous carriers of the variant alleles were combined into one group because the number of women with the homozygous variant genotypes was small. We previously showed that alcohol consumption (15-30 g/d) resulted in increased breast cancer risk compared with never drinkers (15, 16). For the $Ser^{326}Cys$ polymorphism, this association was more pronounced and statistically significant among the women bearing the variant *G* allele (OR, 1.82; 95% CI, 1.06-3.10 relative to nondrinkers with the wild-type genotype). The increased breast cancer risk associated with the $Ser^{326}Cys$ genotype was not observed among women with alcohol consumption of <15 or ≥30 g/d, nor there was any association between alcohol consumption and 7143A/G or 11657A/G genotypes.

For 7143A/G and 11657A/G SNPs, risk was increased among women with the variant *G* allele and BMI > 25 kg/m^2 (7143A/G: OR, 1.47; 95% CI, 1.10-1.96; 11657A/G: OR, 1.41; 95% CI, 1.05-1.88; $P = 0.04$), relative to women with BMI < 25 kg/m^2 and wild-type genotype (Table 3). However, these differences for BMI were primarily driven by differences between individuals heterozygous for the variant allele compared with individuals homozygous for the wild-type allele (7143A/G, *GA* heterozygotes: OR, 1.37; 95% CI, 1.04-1.80; *GG* homozygotes: OR, 1.09; 95% CI, 0.55-2.18; 11657A/G, *GA* heterozygotes: OR, 1.37; 95% CI, 1.03-1.80; *GG* homozygotes: OR, 0.79; 95% CI, 0.36-1.74). These associations were not observed for $Ser^{326}Cys$ polymorphism.

The elevated risk associated with active smoking status, menopausal status, first-degree family history of breast cancer, physical activity, and low fruits and vegetables intake did not differ by any *OGG1* genotype (data not shown).

Discussion

Genotype frequencies for the three SNPs were in agreement with prior studies. None of the SNPs, haplotypes, or diplotypes seemed to influence breast cancer risk, consistent with two previous studies that also did not find any association of the $Ser^{326}Cys$ *OGG1* polymorphism with breast cancer risk (3, 4). There are no other prior studies of 7143A/G or 11657A/G or haplotypes and diplotypes in *OGG1* in relation to breast cancer risk. We selected these SNPs out of all the known polymorphisms in *OGG1* based on the prior results, suggesting they had a role in cancer (17).

Previous studies of $Ser^{326}Cys$ *OGG1* polymorphism showed contradictory results for a number of different cancers (reviewed in ref. 17). In the study of Xu et al. (5), the presence of the Cys allele decreased prostate cancer risk. In that study, the influence of other *OGG1* sequence variants on prostate cancer risk was also analyzed; associations with 7143A/G and 11657A/G variants were found. These results, however, were based on a small number of *GG* carriers. The negative result observed in our study could be due to the higher number of women with *GG* genotypes or due to different effects of these SNPs on breast cancer compared with prostate cancer.

Although some studies suggested reduced repair function with the $Ser^{326}Cys$ variant allele, the evidence is generally inconclusive (reviewed in ref. 17). A recent study (18) concludes that whereas Cys^{326} allele may represent a phenotype deficient in the repair of 8-oxodeoxyguanosine, the deficiency occurs only under the conditions of oxidative stress. There are no reports on the effect of the 7143A/G and 11657A/G *OGG1* polymorphisms on OGG1 protein repair activity.

Several studies investigated gene-environment interactions of the *OGG1* $Ser^{326}Cys$ polymorphism, including the factors known to increase oxidative damage (reviewed in ref. 17). Smoking, alcohol drinking, and high consumption of meat and pickled vegetables was associated with increased risk in carriers of the Cys/Cys genotype in some but not all studies. Our study found increased breast cancer risk for the ^{326}Cys allele among those with alcohol consumption of 15 to 30 g/d. Alcohol drinking may cause oxidative DNA damage through its metabolism via cytochrome CYP450 2E1 that results in generation of reactive oxygen species (19). The association

Table 3. Multivariate-adjusted ORs and 95% CI of BMI interactions for *OGG1* polymorphisms

Genotype	BMI (kg/m^2)	Cases, N	Controls, N	OR* (95%CI)	OR† (95%CI)
Ser^{326}Cys(C/G)					
CC	<25‡	274	319	1.00	1.00
GC + GG	<25	191	225	1.00 (0.77-1.28)	1.03 (0.78-1.35)
CC	≥25	336	325	1.15 (0.92-1.44)	1.23 (0.97-1.57)
GC + GG	≥25	231	209	1.22 (0.95-1.57)	1.29 (0.98-1.70)
7143A/G genotype					
AA	<25‡	344	396	1.00	1.00
GA + GG	<25	118	147	0.91 (0.69-1.21)	0.85 (0.62-1.16)
AA	≥25	398	392	1.11 (0.90-1.36)	1.12 (0.90-1.39)
GA + GG	≥25	174	142	1.33 (1.02-1.74)	1.47 (1.10-1.96)
11657A/G genotype					
AA	<25‡	358	405	1.00	1.00
GA + GG	<25	115	143	0.90 (0.68-1.20)	0.84 (0.62-1.15)
AA	≥25	409	402	1.09 (0.89-1.33)	1.11 (0.89-1.38)
GA + GG	≥25	167	137	1.30 (1.00-1.71)	1.41 (1.05-1.88)

*ORs are adjusted for age.
†ORs are additionally adjusted for lifetime alcohol intake, active smoking status, menopausal status, first degree family history, BMI, physical activity, and fruits and vegetables consumption.
‡Reference group.

among the *OGG1* Ser^{326}Cys polymorphism, alcohol consumption, and cancer risk has been reported previously (20, 21).

In our study, gene-environment interactions for 7143A/G and 11657A/G suggested increased breast cancer risk among the women with high BMI (≥25 kg/m^2) and bearing the variant *G* allele for either SNP. BMI is a risk factor for breast cancer in postmenopausal women because adipose tissue is a source of estrogens, known carcinogens (22). Oxidative stress is one of the proposed mechanisms of estrogen-induced carcinogenesis (23). Increased oxidative stress among women with higher BMI, together with the presence of the variant *G* allele, may result in increased breast cancer risk. Because the association of the 7143A/G, as well as 11657A/G variant, with protein activity has not been studied thus far, the biological mechanisms of our observations are not clear.

Our reported positive interactions between *OGG1* polymorphisms and environmental risk factors should be interpreted with caution. Due to limited power, we collapsed heterozygous and homozygous variant allele groups. However, when we did examine three distinct groups, there was no clear allele dose effect between BMI and the two SNPs. Small numbers limited our ability to investigate moderate alcohol intake (15-30 g/d) by these three genotype categories.

Cases and controls may have differentially recalled their exposure histories (e.g., past alcohol consumption). It is unlikely that this misclassification, if it exists, would differ by genotype status. In addition, it is unlikely that our results can be explained by selection bias because it is unlikely that the selection factors would operate by both genotype and exposure (8). The large study size is a notable strength of this study. However, power was limited for the subgroup analysis. In addition, the population-based study design ensures that the subjects arise from the same source population.

In summary, none of the SNPs, haplotypes, or diplotypes in *OGG1* influenced breast cancer risk. We found some differences between three *OGG1* SNPs and breast cancer risk associated with moderate alcohol drinking and higher BMI. However, understanding the biological function of these SNPs and replication of these results in larger studies is needed to confirm these interactions and to rule out spurious findings.

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